

Newborns' sleep-wake cycle development on amplitude integrated electroencephalography

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Background: To observe the development of neonatal sleep among healthy infants of different conceptional age (CA) by analyzing the amplitude-integrated electroencephalography (aEEG) of their sleep-wake cycles (SWC).

Methods: Bedside aEEG monitoring was carried out for healthy newborns from 32 to 46 weeks CA between September 1, 2011 and August 30, 2012. For each aEEG tracing, mean duration of every complete SWC, number of SWC repetition within 12 hours, mean duration of each narrow and broadband of SWC, mean voltage of the upper edge and lower edge of SWC, mean bandwidth of SWC were counted and calculated. Analysis of the correlations between voltages or bandwidth of SWC and CA was performed to assess the developmental changes of central nervous system of newborns with different CA.

Results: The SWC of different CA on aEEG showed clearly identifiable trend after 32 weeks of CA. The occurrence of SWC gradually increases from preterm to post-term infants; term infants had longer SWC duration. The voltage of upper edge of the broadband decreased at 39 weeks, while the lower edge voltage increases and the bandwidth of broadband declined along with the growing CA. The upper edge of the narrowband dropped while the lower edge risen gradually, especially in preterm stage. The width of the narrowband narrowed down while CA increased.

Conclusions: The SWC on aEEG of 32-46 weeks infants showed a continuous, dynamic and developmental progress. The appearance of SWC and the narrowing bandwidth of narrowband is the main indicator to identify the CA-dependent SWC from the preterm to the

late preterm period. The lower edge of the broadband identifies the term to post-term period.

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Key words: amplitude-integrated electroencephalography; conceptional age; development; newborn; sleep-wake cycle

Introduction

The amplitude-integrated electroencephalography (aEEG) records time-compressed digital EEG trend,^[1] and is widely used in neonatal intensive care units (NICU) for long-term brain function monitoring. This trending modality modifies the raw EEG by filtering frequencies less than 2 Hz and more than 15 Hz, rectifying and smoothing the signal, and uses a semilogarithmic amplitude compression (with a linear display for 0 to 10 mV and logarithmic display for 10 to 100 mV) before displaying it in a time-compressed manner with 6 cm/hour of recording. Researchers in recent years have used aEEG to detect seizures yet the use of recording to directly analyze neonatal sleep-wake cycle (SWC) has not been explored.^[2-6] While most neonatal physicians with a general training in aEEG can rapidly identify severe abnormalities such as burst-suppression and repetitive seizures, they may overlook the absence or disorder of SWC. Clinicians in most NICUs have limited training on sleep analysis of the conventional EEG (cEEG). Prior studies have described some SWC characters of term and preterm infants by cEEG plus multi-parameter recording.^[7] The subjects observed in these studies were similar, mainly comprised of term and moderately preterm infants, thus the relationship between SWC and different conceptional age (CA) was not explored. Moreover, although aEEG is derived from cEEG, its diagnostic standard, including the definition of discontinuous activities, has not been unified.

While under pathological conditions, some diseases are result of the disorder of SWC. In the present study,

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we performed the aEEG to observe the developmental SWC pattern of healthy newborns from 32 to 46 weeks. Recognizing the normal SWC pattern in different CA will help neonatologists to conveniently identify SWC abnormalities by visual analysis, thus may advance neurointensive care practices and predict neurodevelopmental outcomes.^[8]

Methods

Subjects

Twelve-hour bedside cEEG monitoring was carried out in NICU or ordinary neonate ward, and an aEEG was performed for healthy newborns from 32 to 46 weeks CA, between September 1, 2011, and August 30, 2012. Synchronized video and polygraphic recording were used to determine the sleep phases.

This research was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center (2011082312). Written informed consent was obtained from the parents for publication of this case report and any accompanying images. Subject inclusion criteria: 1) CA 32-46 weeks; 2) absence of asphyxia during birth; 3) normal brain ultrasound before EEG recording; 4) no use of sedative drugs before EEG recording; 5) no clinical evidence of convulsions, central nervous system infection or metabolic diseases, and 6) gestational age was calculated with last menstrual cycle. Subject exclusion criteria: the aEEG or EEG results suggested abnormality or any of the following abnormality during hospitalization/referral after discharge: 1) nervous system disorders diagnosed by cranial ultrasound or imaging studies; 2) diagnosis of congenital chromosomal disorders or congenital brain malformations; 3) hypoxic-ischemic encephalopathy, periventricular hemorrhage and periventricular leukomalacia, and 4) sepsis or hyperbilirubinemia. According to different CA, subjects involved in this study were divided into preterm group (CA: 32-36 weeks), full term group (CA: 37-41 weeks) and post-term group (CA: 42-46 weeks), respectively. The 25 babies in preterm group were all uncomplicated preterms, the babies in term and post term groups were preoperation patients for minor surgery.

Experimental method

Nicoletone Monitor (Thirty-two Channels Monitor-one, VIASYS Healthcare, USA) was used in bedside EEG recording for all subjects, in an environmentally controlled situation in which the sound, light, humidity, and tactile stimulation were similar and documented. A 12-hour recording from 7 p.m. to 7 a.m. the next morning was conducted after bath and removal of

newborn's head fat tires. A prewired EEG cap or disc-shaped electrodes were placed according to the 10-20 system modified for neonates. The nine recording leads were FP1, FP2, C3, CZ, C4, O1, O2, T3, T4, respectively. Patient ground and instrument reference were placed in the frontal region. The conductive gel was injected with a flat-syringe through the electrode hole (AP-30B, an electrical conductivity of 36.0 mS/cm, Greentech company Ltd, China). The impedance test was started one minute later and the impedance of the electrode was adjusted to the range of 100-5 K Ω with the following recording parameters: time constant 0.5 seconds, high-frequency filter 70 Hz, notch off. The 9 channel aEEG were generated concurrently. Notable events (care operations) were marked by an EEG technician or nurses during the recording. The electrode impedance was kept in the required range. The interpretation of EEG results was referenced to Current Practice of Clinical Electroencephalography,^[9] and the interpretation of aEEG results was referenced to *Atlas of amplitude-integrated EEGs in the newborn, the second Edition*.^[10] We defined a broadband as a "periods with broader bandwidth", a narrow band as a "the narrower parts of the trace", according to the definition of Hellstroem-Westas. Periods with broader bandwidth represent more discontinuous activity during quiet sleep (QS), and the narrower parts of the trace correspond to more continuous background during wakefulness or active sleep (AS).^[10] Janjarasjitt et al found that 36-46 weeks CA's newborns first enter the AS period when falling asleep, and then into a QS state,^[11] so we define a single SWC as a "combination of a narrowband followed by a broadband".

Data collection and analysis

Data collection, analysis and statistics were performed by two specific EEG analysts. The SWC of newborns was analyzed, counted and documented from one of the bipolar aEEG channel FP1-C3 after removal of artifacts. The following data were obtained: 1) duration of each complete SWC which reflects the stability of SWC; 2) number of SWC repetition within 12 hours which reflects the maturity of SWC; 3) duration of each narrow and broadband which presents the length of wakefulness to AS and QS phases respectively, and 4) percentage of narrow and broadband duration in every SWC which shows the ratio of wakefulness to AS and QS phases. Three SWCs from each patient were selected by random number table method, the following data were collected: 1) voltage of the upper edge which is combined of the highest voltage points: mean voltage of maximum amplitude of burst in discontinuous activities, including trace discontinuous and trace alternant, or the maximum amplitude in continuous

activities; 2) voltage of lower edge which is combined of the lowest voltage: mean voltage of minimum amplitude of inter-burst interval (IBI) in discontinuous activities or minimum amplitude in continuous activities; 3) bandwidth which indicates the distance between upper edge and lower edge is calculated from the mean difference between the value of maximum and minimum amplitude in a same burst-IBI period in discontinuous activities, or the mean difference between the value of maximum and minimum amplitude at the same time point in continuous activities.

Statistical analysis

Calculated mean data were obtained from each subject. Discrete data were assessed by χ^2 test. Quantitative data were described as median (inter-quartile range). Comparisons between groups were performed by using nonparametric tests: Kruskal-Wallis test when all groups were considered as a whole and Wilcoxon rank-sum test when they were compared pairwise. The Spearman correlation analysis was performed between CA and the changes of voltage and bandwidth. Statistical analyses were performed using Sigmaplot 10.0 software (Systat). Statistical significance level was 0.05.

Results

Clinical data

A total of 371 EEG recordings were obtained from 124 neonatal infants, 75 cases among these recordings were retained according to the exclusion criteria, with 25 cases from each group. No statistical difference was found between male and female cases in each group ($\chi^2=0.11$, $P=0.944$) (Table 1).

Occurrence and duration of SWC on aEEG

Data analysis of aEEG revealed that the number of SWC occurrence gradually increased from preterm to post-term infants, which suggested that the SWC reproducibility was improving with maturity ($P<0.001$).

The duration of a single SWC apparently prolonged from preterm to term and then reduced in the post-term. Thus, the term infants had longer duration of single

SWC than the other two groups (both $P<0.001$). The duration and ratio of broad and narrowband indicated longer wakefulness to AS and QS phases in term infants than those in preterm and post-term; but only statistic difference between preterm and post-term groups was found (Table 1).

The voltage of SWC on aEEG

The narrow bandwidth narrowed from preterm to term period. During the term period, the lower edge of broadband was elevated significantly with the voltage higher than 5 μV , while the upper edge showed also sinusoidal changes. During this stage, the lower edge voltage of both narrow and broadband was higher than 5 μV , which indicated a matured EEG development. The SWC characteristics of different CA showed identifiable features: the preterm infants had wider narrowband than the other two groups, the broadband looks like "a suddenly enlarged spindle", the narrow bandwidth of term infants became narrower than the preterms and lower edge voltage of the broadband was mainly higher than 5 μV . Among post-term infants, the lower edge of the broadband significantly increased and broad bandwidth became narrower with a shape similar to an "arch" (Fig. 1).

Data analysis of narrowband and broadband voltages

Preterms had much higher upper edge and lower lower edge of both broad and narrowband than the other two groups. The lower edges of broad and narrowband gradually increases. The upper edge of narrowband gradually decreases. A narrowing trend of both broad and narrow bandwidth appeared during the transition from preterm to post-term development. A more pronounced divergence on the width of broadband and narrowband was readily apparent during every stage (Table 2).

Correlations between voltages and bandwidth of SWC with CA

The upper edge of broadband maintains at levels during the early stage and a sudden decrease appears at 39 weeks, subsequent changes were hardly detectable (Fig. 2A). The lower edge of broadband showed a trend to increase

Table 1. The characteristics of occurrence and duration of SWC on aEEG

Groups	Infant (n)	Gestational age (d)*	Birth weight (g)*	Occurrence of SWC†	Duration of SWC (min)†	Duration of broadband (min)†	Ratio of broadband (%)†	Duration of narrowband (min)†	Ratio of narrowband (%)†
Preterm	25	240 (224-256)	2340 (2045-2840)	7.0 (6.3-7.3)	66.0 (45.8-79.0)	18.0 (16.0-23.5)	32.0 (26.1-44.5)	38.5 (24.8-56.3)	68.0 (55.5-73.9)
Term	25	274 (259-292)	2760 (2076-3900)	8.0 (7.0-9.0)‡	85.5 (62.5-99.5)‡	29.5 (23.0-35.1)‡	37.3 (31.5-44.7)	48.0 (41.5-56.0)**	62.7 (55.3-68.5)
Post-term	25	311 (294-324)	3685 (3040-4440)	9.0 (8.0-10)§	51.0 (43.0-62.3)§	19.5 (15.0-26.3)§	41.5 (36.1-46.2)¶	29.0 (20.0-37.3)§	58.5 (53.6-63.9)¶

SWC: sleep-wake cycle; aEEG: amplitude-integrated electroencephalography. *: median (range); †: median (95% confidence interval); ‡: term vs. preterm, $P<0.001$; §: post-term vs. term, $P<0.001$; ||: post-term vs. preterm, $P=0.007$; ¶: post-term vs. preterm, $P=0.003$; **: term vs. preterm, $P=0.048$.

together with CA ($r=0.938, P<0.001$), with a marked rise at 44 weeks. The bandwidth of broadband showed a declining trend from the preterm to term stages (Fig. 2B) because of the decrease of upper edge and the increase of lower edge. From 42 weeks to 46 weeks, the bandwidth had no obvious changes, although the lower edge still increases slightly. The upper edge of narrowband dropped progressively (Fig. 2C). A strong

negative correlation could be found between the upper edge and the CA ($r=-0.950, P<0.001$). The lower edge of the narrowband gradually risen, especially during preterm stage (Fig. 2C), and a positive relationship with CA ($r=0.656, P<0.001$) was shown. The width of the narrowband tends to be narrowing while CA increased ($r=-0.946, P<0.001$) because of the simultaneously declining of the upper edge along with rise of the lower

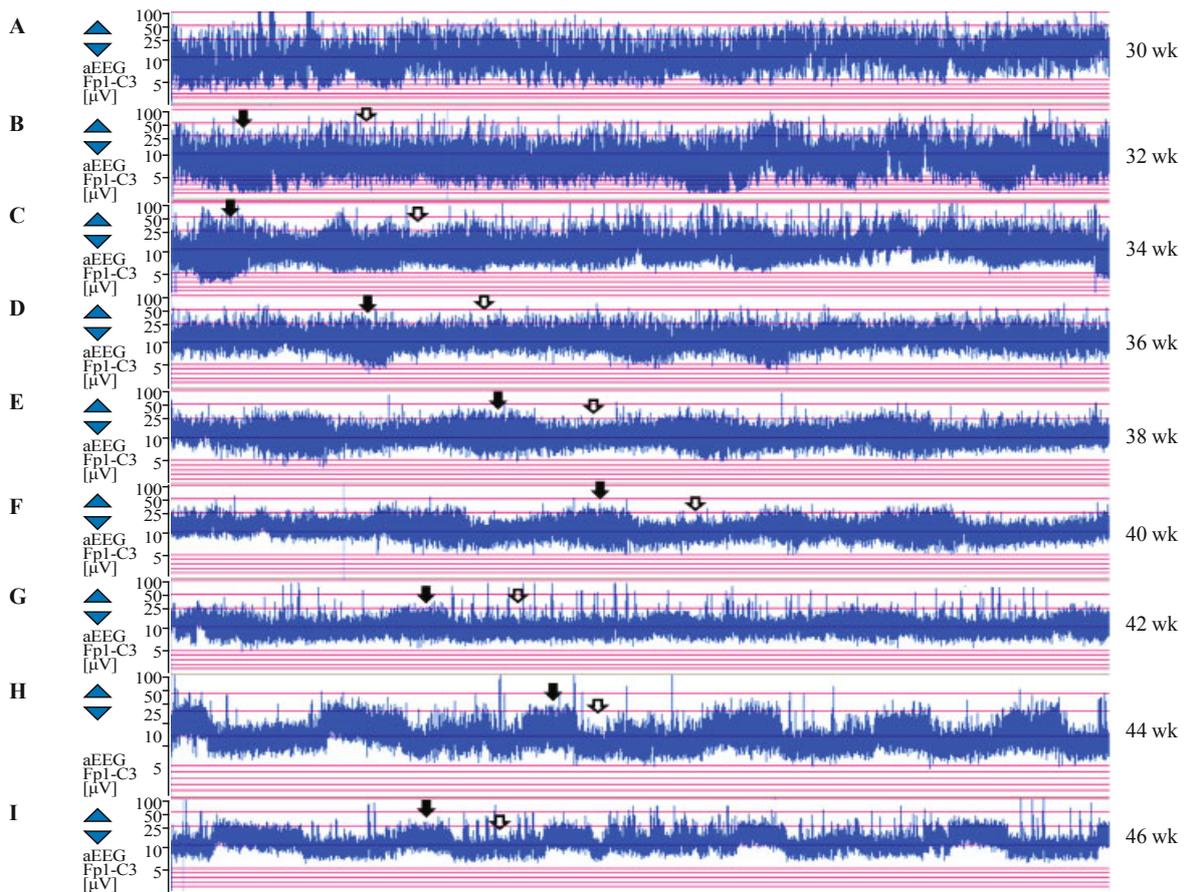


Fig. 1. Typical aEEG traces of different CA. The aEEG presents with a paper speed of 6 cm/h, high filter 15 Hz, low filter 2 Hz. The SWC shows different graphic features at different ages. **A:** Before 32 wk CA, no periodic variation can be seen in both upper and lower edge, SWC is visually unrecognizable on aEEG; **B:** After 32 wk, SWC can be identified; **C:** The narrow part (black arrow) starts to appear from 32 weeks, but the periodic trend cannot be seen until 34 wk, with the lower edge rising above 5 μV at this age; **D:** The narrowband becomes more narrow at 36 wk, while most of the lower edge of broadband (hollow arrow) still remains below 5 μV , thus the shape of broadband looks like a suddenly enlarged "spindle"; **E:** During the age of 38 weeks, the narrowband also remains narrowing due to the elevation of the lower edge, most part of the lower edge voltage of broadband were above 5 μV ; **F:** Up to 40 weeks, few changes could be seen in the narrowband, while the lower edge of broadband steadily elevates, the lower edge voltage of initial part of broadband becomes higher than narrowband; **G-I:** From 42 weeks to 46 weeks, the lower edge inclines until both the upper and lower edge of broadband are above the narrowband, now the "spindle" shape is replaced by the "arch" shape. aEEG: amplitude-integrated electroencephalography; SWC: sleep-wake cycle; CA: conceptual age.

Table 2. Changes in voltage and bandwidth of broadband and narrowband on aEEG [median (interquartile range)]

Groups	Infant (n)	Broadband			Narrowband		
		Upper edge (μV)	Lower edge (μV)	Bandwidth (μV)	Upper edge (μV)	Lower edge (μV)	Bandwidth (μV)
Preterm	25	45.04 (43.49-48.72)	5.00 (4.25-5.33)	41.44 (38.29-43.85)	27.73 (25.18-31.48)	6.44 (5.23-7.66)	20.47 (17.57-25.52)
Term	25	28.83 (26.39-42.47)*	6.68 (6.41-7.15)*	21.78 (19.31-36.18)*	19.02 (18.08-20.79)*	7.61 (6.87-8.07)†	12.10 (11.24-13.19)*
Post-term	25	29.68 (26.10-31.40)†	9.53 (7.78-11.08)‡	19.13 (18.24-21.04)‡§	15.16 (12.79-16.29)‡	8.03 (7.70-8.45)†	6.73 (4.68-7.92)‡

aEEG: amplitude-integrated electroencephalography. *: term vs. preterm, $P<0.001$; †: post-term vs. preterm, $P<0.001$; ‡: post-term vs. term, $P<0.001$; §: post-term vs. term, $P=0.009$; ||: term vs. preterm, $P=0.005$; ¶: post-term vs. term, $P=0.003$.

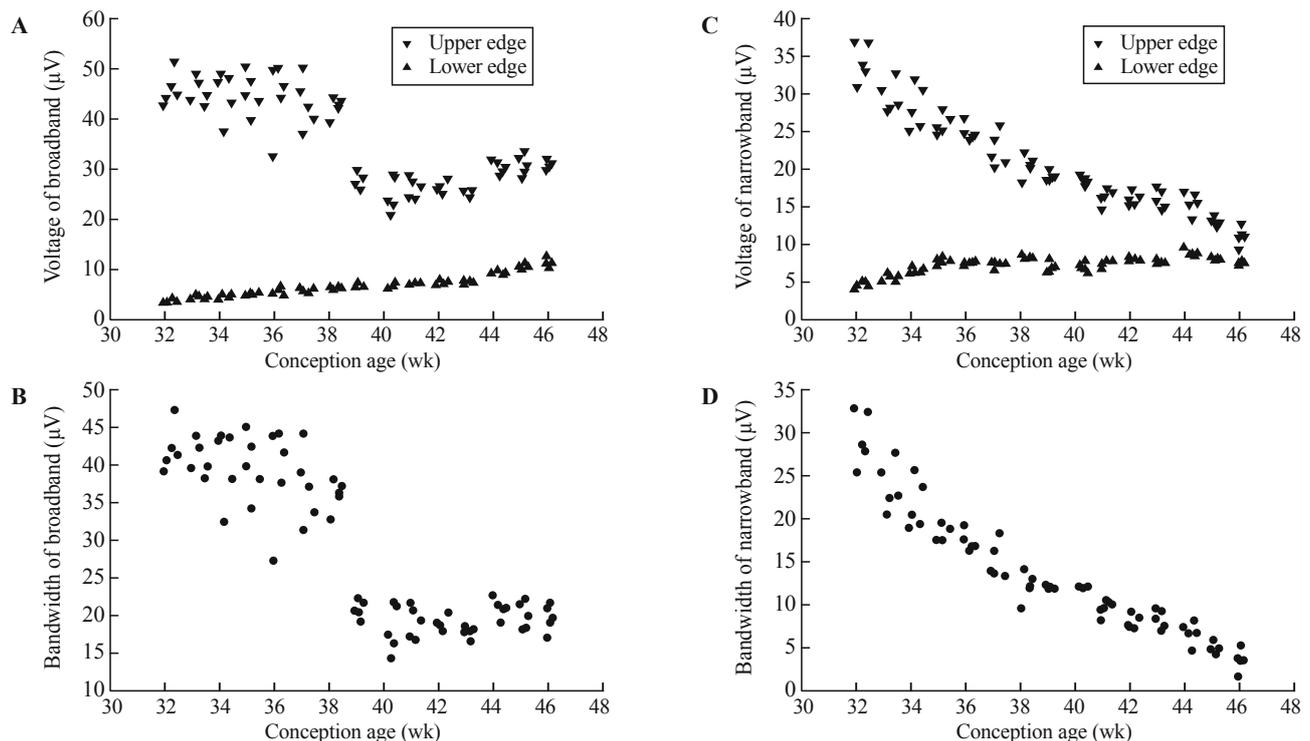


Fig. 2. The voltage and bandwidth of broadband and narrowband. **A:** The upper edge of the broadband is maintained at the level of early stage and a sudden decrease appears at 39 wks (▼). Lower edge of broadband shows an increasing trend and a marked rise at 44 wks (▲); **B:** The bandwidth of broadband shows a declining trend from preterm to term stages and no overt changes in post-term stage; **C:** The upper edge of narrowband progressively drops (▼) while the lower edge of the narrowband gradually rises, especially during the preterm stage (▲); **D:** The width of the narrowband tends to decrease with conception age increases.

edge (Fig. 2D). With increase of CA, the cEEG activity developed from discontinuous to continuous pattern and from low voltage to high voltage. Some characteristics in different CA newborns are shown in Fig. 3.

Discussion

The multi-channel physiological EEG monitoring is commonly used in studying SWC. Using multi-channel EEG monitoring technology, Janjarasjitt et al^[11] found 36-46 weeks CA's newborns first entered the AS period when falling asleep, and then into a QS state, in which the transitional sleep or indeterminate sleep was mixed. Studies have found that sleep characteristics are significantly different not only between the preterm infant group and the full-term group, but also between preterm infant group and the nearly full term infant group.^[12] Compared with EEG with multi-channel parameter, the aEEG is a more straight-forward methodology, especially for clinical doctors who lack of systematic EEG training. Some studies have shown that aEEG and cEEG are consistent in determining the neonatal EEG background activity.^[13] We aimed to identify a simpler and more convenient method to interpret SWC so that we chose aEEG for monitoring SWC. In

this study, we chose the uncomplicated preterms, the term and post term babies only need minor surgery to minimize the sickness impact to SWC.

Studies of preterm infants' SWC less than 30 weeks CA have not been widely reported, although it has been suggested that the predictable sleep state transitions occur among preterm infants by 27-30 weeks gestational age,^[14] but the SWC was not observed in all their subjects. Some defined SWC as smooth sinusoidal variations, mainly in the minimum amplitude,^[10] while Kidokoro et al^[15] defined SWC at least three consecutive cycles in a 5-hour aEEG recording and the volatility fluctuation of the aEEG lower edge $>2 \mu\text{V}$. We defined SWC according to the latter, more stringent definition. In our study, the identification of SWC in CA preterm babies before 32 weeks was unclear on aEEG, only some fluctuation on lower edge could be observed, without periodic changes. An identifiable SWC first emerged among the 32 weeks CA infants, which was the main reason for choosing the 32 weeks CA as an initiating age group. There was a wide range of CA in this study for better estimation of the consecutive changes on aEEG.

We found that the development of SWC from preterm to post-term stages could be easily recognized

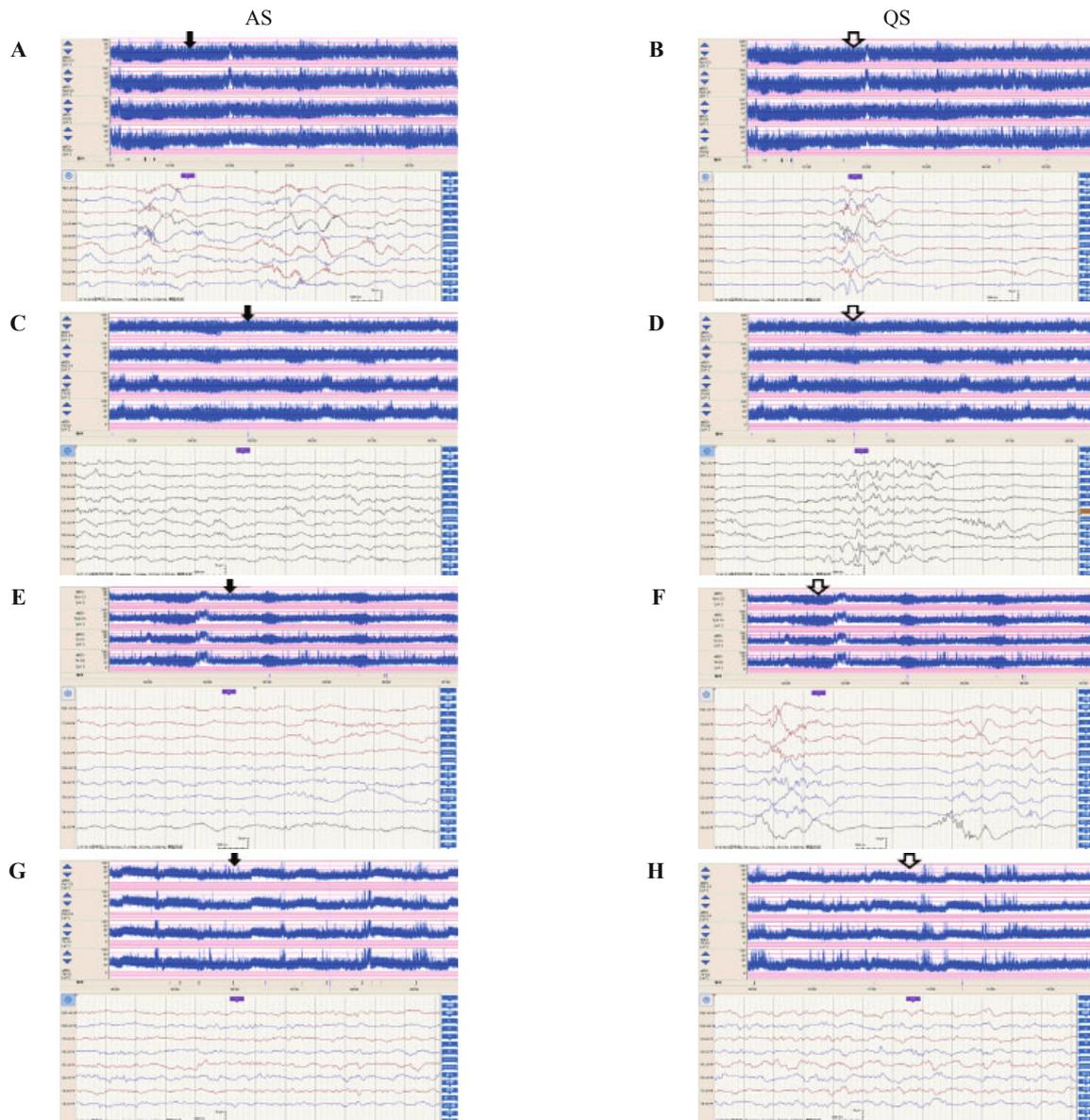


Fig. 3. The SWC evolution on aEEG and cEEG. **A:** The paroxysmal high voltage delta activities plus TA under AS state contribute to a wide narrow bandwidth (black arrow) of 32 wks CA (the cEEG page is timely synchronized with the light blue cursor on aEEG, similarly hereafter); **B:** The TD in QS state leads to a wide broad bandwidth (hollow arrow) of 32 wks CA; **C:** The continuous activities in AS state with evident voltage decrease render the narrow band divergence from the broadband of 35 wks CA; **D:** TA and TD allow the broadband remain wide bandwidth of 35 wks CA; **E:** The voltage of AS state becomes even lower, which makes a narrowing narrowband of 39 wks CA; **F:** CSWS replaces part of the TA and elevates the lower edge of the broadband of 39 weeks CA; **G:** The voltage of AS state remains low and the narrowband maintains narrow for infants at 44 wk CA; **H:** CSWS dominates the QS sleep states and makes the broadband a "arch" shape of infants at 44 wks CA. aEEG: amplitude-integrated electroencephalography; cEEG: conventional electroencephalography; SWC: sleep-wake cycle; CA: conceptional age; TA: trace alternant; TD: trace discontinuous; AS: active sleep; QS: quiet sleep; CSWS: continuous slow-wave sleep.

from aEEG trace and showed a gradually involving trend. Comparative sleep study results from other authors suggested that the sleep cycle of full term newborns showed ultradian rhythm, with the duration of each cycle lasts about 30-70 minutes,^[16] which differed from our observation of the SWC duration, which lasts between 43.0-99.5 minutes. The difference may come from the methodology and definition of SWC. The 30-70

minutes cycle the author mentioned above doesn't include the wakefulness period, this leads to the difference.

Except for the stability and repeatability improving with maturity, the most important developmental characteristics are the changes of voltage and bandwidth of broadband and narrowband which allowed readily identification of maturity easier. In this study, the sample taking points of upper and lower edge were different

from cEEG which was more reasonable for aEEG visual analysis. It was more accurate than only observing the changes of lower edge.^[10] During the preterm stage, the most obvious changes were the narrowing of the narrowband which was correlated with CA, which coincides with Kato et al's study.^[17] We could observe a dramatic decrease of the upper edge of the narrowband and an increase of the lower edge until term stage. The upper edge of broadband maintains in levels at early stage and a sudden decrease appeared at 39 weeks. About cEEG, a sharp reduction of discontinuous patterns may explain clearly the sudden upper edge voltage decline of broadband, which led to a narrowing broadband width at the same time.

The reason that the aEEG reflects the SWC so clearly in neonatal period is that the cEEG development from preterm to post-term age is mainly the change of continuity and voltage according to our clinical observations. With increasing of CA, the cEEG activity developed from discontinuous to continuous pattern, from low voltage to high voltage, which both can be clearly reflected on the aEEG. The appearance of SWC and bandwidth of narrowband were the main characteristics to identify the consistency between SWC and CA from preterm to late preterm period and the lower edge of broadband is relevant to identifying the CA-dependent SWC from term to post term period (Fig. 3).

The absence or disorder of the normal sleep cycle is a serious abnormality in cEEG. Pezzani et al^[18] found that within 24 hours of a full-term birth, infants who lacked normal sleep cycle in cEEG recordings had poor prognosis: the majority died or had significant complications, and only a few could have normal development. The absence of SWC has been reported to have prognostic value for full term neonates with asphyxia.^[19,20] Kidokoro et al^[15] found that absence of SWC was related to brain injury in preterm infants within 24-hour after birth. Pathological status can also lead to the segment change of SWC according to our clinical observation. For neonatal physicians, identifying SWC timely and correctly is crucial to develop treatment strategies, to evaluate the trend of recovery, especially in the situation of negative morphological finding of the nervous system. On the other hand, the correlation between SWC development and CA is also valuable to evaluate the maturity of nervous system. A series of SWC observation of the same patient may be more significant to assess the nervous system development process. In these cases, aEEG will be a simple detection to address these purposes.

On the other hand, the aEEG has its disadvantages in SWC interpretation. It may not be of most concern of clinical doctors, but the indeterminate sleep state, which accounted for 10%-15% of a whole SWC, is not

recognized clearly from aEEG. Meanwhile, the aEEG may not be relevant anymore for SWC analysis after the neonatal period, while the sleep assessment will rely on the characteristic sleep waves such as Vertex Sharp, Spindle and K-complex at that time.

In conclusion, we have illustrated that the development of cEEG background activity of different CA newborns is the foundation of aEEG SWC, which displays the developmental changes of central nervous system from immature to mature. Developmental characteristics of SWC on aEEG may also serve as parameters to observe the effects of treatment and drugs on SWC.^[21]

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Contributors: Li XF proposed the study and wrote the first draft. Zhou YX analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. Zhang L is the guarantor.

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